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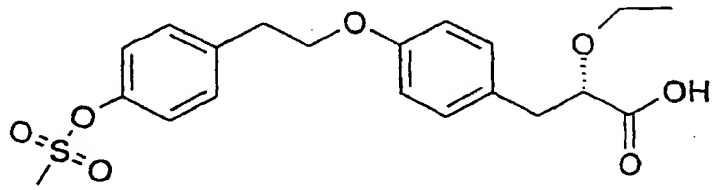
Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMMINUTED FORM OF (S)-2-ETHOXY -3-[4-(2- {4-METHANESULFONYLOXYPHENYL} ETHOXY) PHENYL] PROPANOIC ACID



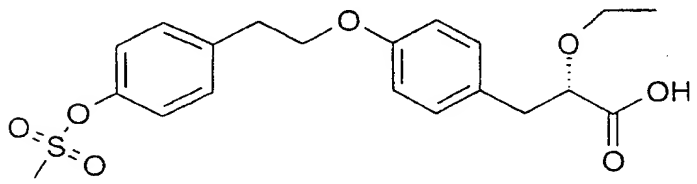
(I)

(57) Abstract: The present invention relates to a reduced particle size form of the compound (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid, as shown in formula (I), or a pharmaceutically acceptable salt thereof or a solvate of either thereof. The invention also concerns methods of treating one or more conditions associated with Insulin Resistance Syndrome using the reduced particle size form of the compound, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in one or more of said conditions. The invention further concerns pharmaceutical compositions containing the reduced particle size form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient, as well as processes for the manufacture of the reduced particle size form of the compound, or a pharmaceutically acceptable salt thereof.

WO 01/40169 A1

Comminuted Form of (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl} ethoxy)phenyl] propanoic acid

The present invention relates to a reduced particle size form of the compound (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid, as shown in the formula I below



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, or a pharmaceutically acceptable salt thereof or a solvate of either thereof. The invention also concerns methods of treating one or more conditions associated with Insulin Resistance Syndrome using the reduced particle size form of the compound, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in one or more of said conditions. The invention further concerns pharmaceutical compositions containing the reduced particle size form of the compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof, as an active ingredient, as well as processes for the manufacture of the reduced particle size form of the compound, or a pharmaceutically acceptable salt thereof.

In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance from the point of view of manufacture of pharmaceutical formulations comprising the active compound.

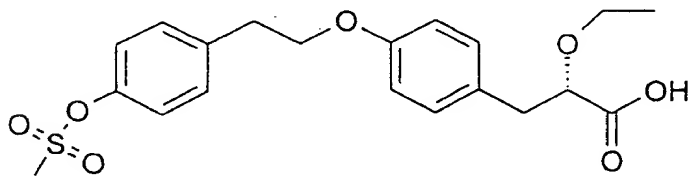
The above compound is useful in treating metabolic disorders, such as Insulin Resistance Syndrome (IRS), defined as reduced sensitivity to the actions of insulin in the whole body or individual tissues such as skeletal muscle, myocardium, fat and liver prevail in many individuals with or without diabetes mellitus. IRS refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinemia, possibly type II diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidemia observed as deranged lipoprotein levels typically characterised by elevated VLDL (very low density lipoproteins) and reduced HDL (high density lipoproteins) concentrations and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In type II diabetes mellitus these atherosclerosis related conditions cause up to 80% of all deaths.

In clinical medicine there is awareness of the need to increase the insulin sensitivity in IRS and thus to correct the dyslipidemia which is considered to cause the accelerated progress of atherosclerosis. However, this is not a universally defined disease.

We have discovered a reduced particle size form of the compound described above. This provides a basis for the present invention. Significant advantages can arise when the compound of formula I is in a reduced particle size form, for example, in the performance of the compound when it is manufactured so as to achieve uniform formulations with an even loading of active ingredient within as well between batches. In addition reductions in particle size are typically associated with increased dissolution rates when administered orally and improved oral bioavailability, when oral bioavailability is limited by the dissolution rate of the active ingredient.

Accordingly provided in the present invention is a reduced particle size form of (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid, as shown in the formula I below



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or a pharmaceutically-acceptable salt or a solvate or either thereof.

By the use of the term "reduced particle size" we refer to solid Compound 1, or a pharmaceutically-acceptable salt thereof, or a solvate of either thereof, reduced by suitable processing techniques to a solid of smaller particle size and, consequently, greater surface area. Any number of processing techniques known in the pharmaceutical field may be used to reduce solid particle size, such as grinding, milling and micronising, reference should be made

to Remington: The Science and Practise of Pharmacy, 19th Ed., pages 1598-1602, for a more exhaustive review.

By use of the term "solvated" we include hydrated.

Accordingly presented as a further feature of the invention is a process for the preparation of a reduced particle size form of the compound of formula I, or a pharmaceutically-acceptable salt or a solvate of either thereof, comprising comminuting a solid form of the compound of formula I, or a pharmaceutically-acceptable salt or a solvate of either thereof, for a sufficient period until the desired size of particle of the compound of formula I, or a pharmaceutically-acceptable salt or a solvate of either thereof, is generated.

The range of particle sizes preferred in this invention start from, in increasing preference, moderately fine powder, fine powder, very fine powder, microfine powder to, most preferably, superfine powder.

The above references to particle sizes are taken from the British Pharmacopoeia 1993, Volume II, Appendix XVII B, A193, and are reproduced below for reference.

Moderately fine powder

A powder all the particles of which pass through a sieve with a nominal mesh aperture of 355μm and not more than 40.0% by weight pass through a sieve with a nominal mesh aperture of 250μm.

Fine powder

A powder all the particles of which pass through a sieve with a nominal mesh aperture of 180μm and not more than 40.0% by weight pass through a sieve with a nominal mesh aperture of 125μm.

Very fine powder

A powder all the particles of which pass through a sieve with a nominal mesh aperture of 125μm and not more than 40.0% by weight pass through a sieve with a nominal mesh aperture of 45μm.

Microfine powder

A powder of which not less than 90% by weight of the particles pass through a sieve with a nominal mesh aperture of 45μm.

Superfine powder

A powder of which not less than 90% by weight of the particles pass through a sieve with a nominal mesh aperture of 10μm.

The particular sieves to be used in determining the particle size are described in British Pharmacopoeia 1993 Volume II, Appendix XVIIB, A193-A194, which part is incorporated herein by reference.

A feature of the invention is a reduced particle size form of a compound of formula I, as described above, for use in medical therapy.

According to a further feature of the invention there is provided a pharmaceutical composition which comprises a reduced particle size form of a compound of formula I, as described above, in association with a pharmaceutically-acceptable diluent, adjuvant or carrier.

The composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The amount of the reduced particle size form of a compound of formula I, as described, above that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.01 mg to 50mg of active agent compounded with an appropriate and convenient amount of excipient(s) which may vary from about 20 to about

99.99 percent by weight of the total composition. Dosage unit forms will generally contain about 0.0001 mg to about 1 mg of an active ingredient.

The invention also includes the use of a Compound of the invention, as described above in the production of a medicament for use in:-

(i) treating dyslipidaemia;

(ii) treating type II diabetes mellitus;

(iii) treating hyperglycaemia;

(iv) treating hyperlipidaemia;

(v) treating hyperinsulinaemia;

(vi) treating arterial hypertension; and/or

(vii) treating abdominal obesity.

The invention also includes a method of producing an effect as defined hereinbefore or treating a disease or disorder as defined hereinbefore which comprises administering to a warm-blooded animal requiring such treatment an effective amount of a reduced particle size form of a Compound of formula I, as described above.

The size of the dose for therapeutic or prophylactic purposes of a reduced particle size form of a Compound of the invention, as described above, will naturally vary according to the nature and severity of the medical condition, the age and sex of the animal or patient being treated and the route of administration, according to well known principles of medicine. Suitable daily doses of the compounds of the invention in therapeutical treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

The comminuted form of the compound of formula I may be administered as a sole therapy or they may be administered in conjunction with other pharmacologically active agents such as a anti-diabetic, anti-hypertensive, diuretic or anti-hyperlipidemic agent.

The invention will now be illustrated in the following non-limiting Examples.

Example 1

Synthesis of (S)-2-ethoxy-3-[4-[[4-(methylsulfonyloxy)phenethyl]oxy]phenyl] propanoic acid

1-(Methylsulfonyloxy)-2-[4-(methylsulfonyloxy)phenyl]ethane

2-(4-Hydroxyphenyl)ethanol (356 g, 2.58 mol, 1.0 eq) was dissolved in methylene chloride (3500 ml) and triethyl amine (653 g, 6.44 mol, 2.5 eq). The mixture was cooled to -20°C. Methanesulfonyl chloride (657 g, 5.74 mol, 2.2 eq) was then added keeping the temperature between -25°C and -15°C. When the conversion was >95% salts were formed which were filtered off and washed with methylene chloride (600 ml). The organic layer was washed first with saturated sodium hydrogencarbonate solution (700 ml) at 20°C followed by water (700 ml). The methylene chloride was evaporated to dryness and the remaining residue was then used in the subsequent step.

Ethyl (S)-2-ethoxy-3-[4-[[4-(methylsulfonyloxy)phenethyl]oxy]phenyl] propanoate

Ethyl (S)-2-ethoxy-3-(4-hydroxyphenyl)-propanoate (325 g, 1.36 mol, 1.0 eq) was dissolved in acetonitrile (2600 ml). When a homogenous solution was formed, potassium carbonate (560 g, 4.05 mol, 3.0 eq) and magnesium sulfate (110 g, (0.2 g/g K_2CO_3)) was added. To the acetonitrile solution 1-(methylsulfonyloxy)-2-[4-(methylsulfonyloxy)phenyl] ethane (ca: 2050 ml (0.3 g/ml, 2.21 mol, 1.65 eq)) was charged and the mixture allowed to react at reflux, 82°C for 24 hours with vigorous stirring. When a conversion >98% was reached the reaction was cooled to room temperature. The remaining salts were filtered of and washed with acetonitrile (800 ml). The filtrate was evaporated to dryness. The oil residue was then used in the subsequent step.

(S)-2-Ethoxy-3-[4-[[4-(methylsulphonyloxy)phenethyl]oxy]phenyl] propanoic acid

To the oil of ethyl (S)-2-ethoxy-3-[4-[[4-(methylsulfonyloxy)phenethyl]oxy]phenyl] propanoate(723 g (71.2% assay), 1.18 mol, 1.0 eq) was added tetrahydrofuran (THF) (3900 ml). When a homogenous solution was formed, water (900 ml) was added. The mixture was cooled to +10°C. Lithium hydroxide solution (390 ml, 4 M, 1.45 eq) was added over 1 hour. The temperature was then raised to +30°C and the reaction allowed to proceed at this temperature for 2-3 hours. The reaction was stopped when the conversion was >99%. Ethyl acetate (500 ml) was added and the mixture cooled to room temperature. The solution was stirred for about 30 minutes and the THF was evaporated off. When about 80-90% of the THF was evaporated water (1900 ml) was added. The evaporation was continued until no THF remained in the mixture. The alkali water solution was then washed with ethyl acetate (1000 ml, 2 × 1250 ml, and 950 ml). The pH of the water solution of (S)-2-ethoxy-3-[4-[[4-(methylsulphonyloxy)phenethyl]oxy]phenyl] propanoic acid was then adjusted to 2.0-2.5 with HCl (aq) (550 ml, 3.0 M). Ethyl acetate (2500 ml) was added and the phases separated. The ethyl acetate solution of (S)-2-ethoxy-3-[4-[[4-(methylsulphonyloxy)phenethyl]oxy]phenyl] propanoic acid was then washed with water (700 ml) and after separation evaporated to dryness. The remaining oil was then used in the following crystallisation

Crystallisation of (S)-2-ethoxy-3-[4-[[4-(methylsulfonyloxy)phenethyl]oxy]phenyl] propanoic acid

The oil from 3 batches of (S)-2-Ethoxy-3-[4-[[4-(methylsulphonyloxy) phenethyl]oxy]phenyl] propanoic acid (1262g, 3.09 mol, 1.0 eq) was dissolved in toluene (2500 ml) at 50°C. When a clear solution was achieved the solution was evaporated to decrease the amount of ethyl acetate present. The volume before evaporation was 6750 ml. Another portion of toluene (2500 ml) was added, the volume after the addition being 7750 ml, and evaporation was continued. A third portion of toluene was then added to the solution, volume before the addition was 6300 ml, the volume after the addition was 8800 ml. The evaporation was continued until an opaque solution was formed, volume 8200 ml. Isooctane (1000 ml) was then added to the solution which had been heated to 40°C. The crystallisation

was initiated by seeding at 40°C. The mixture was vigorously stirred until a slurry was formed. The agitation rate was then decreased. The slurry was left crystallising over night. The slurry was then filtered and washed with toluene: isooctane 5:1 (1800ml). The crystals were then dried under reduced pressure at 40°C.

Example 2

Preparation of Reduced Particle Size Form of Compound 1

Example 2:1:

Compound 1	0.8 g
Hydroxypropyl cellulose LF	24 g
Water	1000 g

Compound 1 was dispersed in 600 g water whilst stirring with a high shear mixer. Hydroxypropyl cellulose LF was added and stirring continued until the suspension was homogenous. The suspension was pumped into a ball mill, equipped with approx. 500 ml 1.0 – 1.5 mm glass beads, using a peristaltic pump at approx. 70 g/min. Milling was performed at 2000 rpm. The first 200 g of the milled suspension was re-charged. The mixer, vessel, hoses and millhouse were rinsed with 400 g water.

Particle size analysis was performed on the suspension before and after milling using a Coulter LS. Mean particle size was measured to 24.93 μm and 7.086 μm respectively.

Example 2:2:

Compound 1	8 g
Hydroxypropyl cellulose LF	24 g
Water	1000 g

Compound 1 was dispersed in 400 g water whilst stirring with a high shear mixer. Hydroxypropyl cellulose LF was added and stirring continued until the suspension was homogenous. The suspension was pumped into a ball mill, equipped with approx. 500 ml 1.0 – 1.5 mm glass beads, using a peristaltic pump at approx. 80 g/min. Milling was performed at 2000 rpm. The first 200 g of the milled suspension was re-charged. The mixer, vessel, hoses and millhouse were rinsed with 600 g water.

Particle size analysis was performed on the suspension before and after milling using a Coulter LS. Mean particle size was measured to 14.79 µm and 7.614 µm respectively.

Example 2:3:

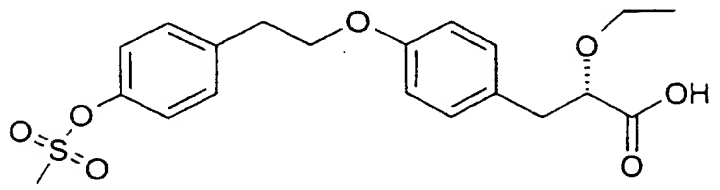
Compound 1	5 g
Hydroxypropyl cellulose LF	600 g
Water	8000 g

Compound 1 was dispersed in 4000 g water whilst stirring with a high shear mixer. Hydroxypropyl cellulose LF was added and stirring continued until the suspension was homogenous. The suspension was pumped into a ball mill, equipped with approx. 500 ml 1.0 – 1.5 mm glass beads, using a peristaltic pump at approx. 75 g/min. Milling was performed at 2000 rpm. The first 200 g of the milled suspension was re-charged. The mixer, vessel, hoses and millhouse were rinsed with 4000 g water.

Particle size analysis was performed on the suspension before and after milling using a Coulter LS. Mean particle size was measured to 48.35 µm and 6.822 µm respectively.

CLAIMS

1. A reduced particle size form of either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid, as shown in formula I below



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or a pharmaceutically-acceptable salt thereof or a solvate of either thereof.

2. A reduced particle size form as claimed in claim 1 which is a superfine powder.

3. A reduced particle size form as claimed in claim 1 which is a microfine powder.

4. A reduced particle size form as claimed in claim 1 which is a very fine powder.

5. Use of any substance defined in any one of claims 1 to 4 in medical therapy.

6. A pharmaceutical composition comprising a substance as defined in any claim from 1 to 4 in association with a pharmaceutically-acceptable diluent, adjuvant or carrier.

7. The use of a substance as defined in any claim from 1 to 4 in the production of a medicament for use in treating metabolic disorders.

8. A method for treatment or prophylaxis of conditions associated with reduced sensitivity to insulin, which method comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 4 to a patient having such reduced sensitivity to insulin.

9. A method for treatment or prophylaxis of dyslipidaemia, type II diabetes mellitus, hyperglycaemia, hyperinsulinaemia, arterial hypertension and/or abdominal obesity, which method comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 4 to a patient in need of such treatment or prophylaxis.

10. A process for the preparation of a compound according to any one of claims 1 to 4, comprising crystallising a compound shown by the formula I, or a salt or solvate thereof, or a solvate of such as salt.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02381

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 309/66, A61K 31/192, A61P 5/48, A61P 3/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 9962872 A1 (ASTRAAKTIEBOLAG), 9 December 1999 (09.12.99), page 20, line 25 - page 32, line 17, the claims --	1-10
P,A	WO 9962871 A1 (ASTRA AKTIEBOLAG), 9 December 1999 (09.12.99), claims 1, 32, 33 -- --------	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 March 2001	16 -03- 2001

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02381

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8, 9
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional ...

Claims 8, 9 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/01

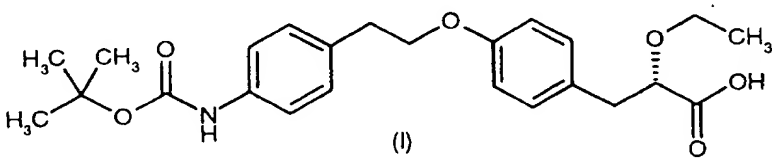
International application No.
PCT/SE 00/02381

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9962872 A1	09/12/99	AU 1182399 A	31/05/99
		AU 4667199 A	20/12/99
		AU 4667299 A	20/12/99
		NO 20006115 D	00/00/00
		NO 20006116 D	00/00/00
		SE 9801992 D	00/00/00
		WO 9962871 A	09/12/99
WO 9962871 A1	09/12/99	AU 1182299 A	31/05/99
		AU 4667099 A	20/12/99
		AU 4667299 A	20/12/99
		BR 9813192 A	29/08/00
		EP 1029424 A	23/08/00
		NO 20006114 D	00/00/00
		NO 20006116 D	00/00/00
		SE 9801990 D	00/00/00
		WO 9962870 A	09/12/99
		AU 1058399 A	24/05/99
		EP 1027769 A	16/08/00
		SE 9801991 D	00/00/00
		AU 1182399 A	31/05/99
		AU 4667199 A	20/12/99
		NO 20006115 D	00/00/00
		SE 9801992 D	00/00/00
		WO 9962872 A	09/12/99

AstraZeneca AB

Microparticles of 3-{4-[2-(4-tert-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid - useful for the treatment of e.g. metabolic disorders, insulin resistance syndrome, dyslipidaemia, hyperglycaemia and arterial hypertension.

Drug Activity: Microparticle; Powder; Antidiabetic; Antilipemic; Hypotensive; Anorectic
Mechanism of Action: Hypoglycemic



(I)

Use: As a microparticle or powder for the treatment of metabolic disorders, insulin resistance syndrome, reduced sensitivity to insulin, dyslipidaemia, type 2 diabetes mellitus, hyperglycaemia, hyperinsulinaemia, arterial hypertension and abdominal obesity (claimed).
Dosage: 0.001 - 50 mg orally. Administration is also topical, vaginal, rectal, parenteral, sublingual, buccal, intravenous, subcutaneous, intramuscular or by inhalation or infusion.
Advantage: None given.
Example: (I) was dispersed in water (600 g) whilst stirring with a high shear mixer. Hydroxypropyl cellulose LF was added and stirring continued until the suspension was homogenous. The suspension was pumped into a ball mill, equipped with approx. 500 ml of 1 - 1.5 mm glass beads, using a peristaltic pump at approx 70 g/min. Milling was performed at 2000 rpm. The first 200 g of the milled suspension was recharged. The mixer, vessel, hoses and millhouse were rinced with water (400 g).
Chemistry: A reduced particle size form of 3-{4-[2-(4-tert-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid (I) or a salt or solvate of (I) are claimed.

16 pages

Drawings 0/0

Authors: Hallgren A; Roos K
Location: Sodertalje, Sweden
Publication Date: 07 June 2001
Document Number: WO200140169-A1
Language: English
Filed: 29 November 2000 as SE2381
Priority: 03 December 1999 SE-001413
Designated States: Regional: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE (ARIPO) (Eurasian) (OAPI) National: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW